73. The transgenic animal of claim 72, wherein said urinary tract-specific regulatory sequences comprise at least one of a 5' urinary tract-specific regulatory sequence.

74. The transgenic animal of claim 73, wherein said urinary tract-specific regulatory sequences comprise a 3' urinary-tract-specific regulatory sequence.--

REMARKS

Claims 1, 5-8, 11-13 and 15-66 are currently pending. Applicants herewith cancel claims 1, 8, 16-44, 48-50, 58-60, and 66 without prejudice or disclaimer and add claims 67-74. Thus, with the entry of this amendment, claims 5-7, 11-15, 45-47, 51-57, 61-65 and 67-74 are active in this case. Particularly, claims 16-44 and 66, directed to non-elected subject matter, are canceled without prejudice or disclaimer for filing in a divisional application. Claims 6, 11, 12, 45-47, 52, 53, 56, 57, 62 and 63 are amended. The addition of "peptide" to claims 45 and 56 is supported in the specification, for example, on page 15, lines 10-12 and page 30, lines 19-21. Claims 67-74 have support in the description on page 15, lines 7-20; page 15, line 31 to page 16, line 2; page 17, lines 25-28; and page 20, lines 5-34. No new matter is added with the new claims or the specification.

Applicants note that the examiner did not consider two documents that were cited on the PCT Search Report by the European examiner and previously submitted by applicants in an Information Disclosure Statement. The document FR 2 717 500 was filed with an English language abstract from the Dialog Database but it appears to have been separated from the file. Applicants herewith provide a further copy of this abstract attached to this French patent document for consideration by the examiner. Additionally, the examiner did not consider an abstract by William Velander cited in the PCT Search Report by the European examiner as a "P, X" document. This document was not placed on the internet by Virginia Tech Intellectual Properties, Inc. until the beginning of 1998 as evidenced by the Disclosure No.: 98-011. Applicants enclose a copy of the PCT Search Report for the examiner's convenience. It is requested that the examiner consider these previously submitted documents and indicate such consideration on the attached PTO-1449 form.

1. Sequence Listing

The examiner objects to the specification for failing to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequences. Applicants herewith comply with this requirement by submitting the Sequence Listing in computer readable form, by amending the specification to insert the required references to SEQ ID NOS of the Sequence Listing filed concurrently herewith, to indicate the insertion point for the Sequence Listing, and to effect the necessary changes in pagination. Applicants respectfully request the withdrawal of this objection.

2. Rejections under 35 U.S.C. § 112, first paragraph

The examiner rejects claims 1, 5-8, 11-15 and 45-65 as not being enabled for any and all transgenic animals whose genome comprises any and all 5' regulatory regions and any and all genes encoding any and all exogenous proteins. The examiner contends that producing transgenic animals is an unpredictable art in obtaining the desired phenotype of expressing a protein in the urine at detectable levels. Additionally, the examiner contends that the expression of a transgene in a mouse is not predictable of expression in another non-human animal. Applicants respectfully disagree with the examiner's allegation. Absolute predictability is not required for enablement. The issue is one of whether it would require undue experimentation to arrive at the invention given the teachings in the specification. Applicants assert that it would not.

First, applicants provide data within the present specification in Figure 5 and Table III that shows that protein C was produced in the urine of both transgenic mice and pigs. Thus, by following the teachings in the specification, it is possible to arrive at the invention that encompasses more than one type of animal.

Additionally, it was known prior to the filing date of the present invention that many researchers were producing many different proteins in a broad range of hosts. See Lubon *et al.*, *Transfusion Medicine Reviews* Vol. X, No. 2, pp. 131-143 (1996), attached as Appendix A. Tables 1, 2 and 3 of Lubon *et al.* provide support for this statement by surveying the transgenic literature prior to the filing date of the present invention. Likewise the specification on page 32, line 10 to page 34, line 31, discloses numerous publications that disclose the expression of many different proteins in different species of transgenic animals. It is applicants' position that a person skilled in the art at the time of filing the present

invention would have been guided by these teachings and would have been provided with methods, tools and constructs to produce different proteins in a range of transgenic animals. Thus, the required experimentation was not undue.

Lubon *et al.* in Table 1 shows the different tissues and body fluids of a number of different host organisms in which various blood proteins are expressed. Thus, it is well within the skill of the artisan to produce proteins in many different tissues and bodily fluids of transgenic organisms using the appropriate regulatory sequences which will direct the protein to the tissue in which it is to be expressed. It would only require trial and error experimentation to select appropriate DNA constructs, inject the constructs into the animals and test for expression of correctly processed proteins in the tissues. Undue experimentation is not required for such selection.

Additionally, it would not require undue experimentation to express any protein that is known to degrade and detoxify organic material in the urine of a broad range of transgenic animals by applying applicants' description to known proteins utilizing the skill of the artisan in the field of transgenics.

The examiner also alleges that undue experimentation is required to select regulatory sequences that will be useful in expressing proteins in the urine of animals other than mammals. Applicants direct the examiner to the specification on page 33, line 36 to page 34, line 6 that refers to a 1997 Houdebine edited book that discloses methods and tools for producing transgenic animals other than mammals.

The examiner states that in the absence of working examples for regulatory regions other than WAP, the breadth of the claims to any and all 5' regulatory regions, the scope of the invention is not supported. Under the first paragraph of 35 U.S.C. 112, the specification is presumptively accurate unless there are reasons to doubt the truth of an assertion contained therein. In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971). In re Brana, (Fed. Cir. 1995) (holding that the Utility Examination Guidelines are applicable to rejections under 35 U.S.C. § 112, first paragraph). Therefore, the specification cannot be found non-enabling merely because some statements in the specification are not supported by working examples. Indeed, the courts have found that a specification may be enabling without any working examples at all. Ex parte Nardi, 229 USPQ 79 (BPAI 1986).

Applicants believe that they have shown that the skill of the artisan in the transgenic field is very high and that the experimentation required to determine the appropriate

conditions and parameters, such as, choice of host, regulatory sequence, and DNA constructs, to obtain expression from a founder is not undue but well within the skill level. All that is required is screening methods to select for the appropriate combinations of parameters and the detection of the expressed protein in the urine of the animal.

As a result of the above arguments, applicants request that this rejection of claims 1, 5-8, 11-13, 15 and 45-65 (now claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74) be withdrawn.

3. Rejections under 35 U.S.C. § 112, first paragraph

The examiner rejects claims 52, 53, 62 and 63 as not being adequately described in the specification. Applicants respectfully disagree with the examiner and direct the examiner's attention to page 20, line 35 to page 29, line 31 and page 42 (Example 3) that discloses the source of the genes from which the expression regulatory sequences are obtained. Publications disclosing the genes encoding these proteins are cited in the specification or were known prior to the filing date of the present invention. The citation of appropriate publications and utilizing sequences from known sequenced proteins is sufficient to overcome this rejection. It is not necessary for applicant to disclose what is known to persons skilled in the art. A "patent need not disclose, and preferably omits, what is well known in the art." Hybritech v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986). If the examiner requires additional evidence of the known sequences of the recited proteins, applicants request that the examiner request this information. It is requested that this rejection be withdrawn in view of these arguments.

4. Rejections under 35 U.S.C. § 112, second paragraph

The examiner rejects claims 1, 5-8, 11-13, 15 and 45-65 as being indefinite because she believes that the term "kidney-specific promoter" is unclear. The claims are amended and now only claims 53, 63, 68 and 72 contain this term. Applicants respectfully disagree with the examiner because the claims are interpreted in light of the specification. The term is given its art recognized meaning, which is that the regulatory sequences or promoter is capable of expressing proteins in the cells of the kidney. The specification on page 20, lines 13-30 supports this interpretation.

Claim 64 has been amended to overcome the obvious typographical error.

In view of these arguments and amendments, it is requested that this rejection be withdrawn.

5. Rejections under 35 U.S.C. § 102

The examiner rejects claims 45-49, 51, 52, 54-59, 61, 62, 64 and 65 as being anticipated by Sun *et al.* (U.S. 5,824,543 - the '543 patent) or Sun *et al.* (WO96/39494 – the '494 patent) because the examiner alleges that both the '543 patent and the '494 patent disclose transgenic mice whose genome comprises a uroplakin promoter operably linked to a gene of interest. The examiner further alleges that the protein is expressed in the urothelium of the mouse and is detectable in the urine.

Applicants have amended the claims so that independent claims 45 and 56 are directed to a method of producing in the urine of a non-human transgenic animal a protein or a peptide that degrades and detoxifies organic material and the transgenic animal that is used in the method, respectively. Previous claims 1 and 8 contained this feature and were not rejected by these two patents. Neither of the Sun patents discloses the transgenic expression of a protein or a peptide that degrades or detoxifies organic material, which is why they were not utilized to reject claims 1 and 8. In view of these amendments, it is requested that this rejection be withdrawn.

6. Rejections under 35 U.S.C. § 102

The examiner rejects claims 45-49, 51, 54-59, 61, 64 and 65 as being anticipated by Lubon *et al.* ("Lubon") because the examiner alleges that the '327 patent discloses a transgenic mammal comprising a mammary gland specific promoter to express a protein or a peptide in the milk or urine of a mammal to isolate the protein or peptide. For the same reasons as argued in the rejection of the claims over both of the Sun patents, Lubon does not disclose expressing a protein or a peptide that degrades or detoxified organic material, but rather is directed to the expression of factor VIII, a blood protein. All of the claims are now directed to the expression of a protein or a peptide that degrades or detoxified organic material. For the same reasons as set forth above, it is requested that this rejection be withdrawn.

7. Rejections under 35 U.S.C. § 103

The examiner rejects claims 1, 5-8, 11-13, 15, 45-52, 54-62, 64 and 65 as being obvious over the combination of either Sun *et al.* (U.S. 5,824,543 - the '543 patent) or Sun *et al.* (WO96/39494 – the '494 patent) in view of Lubon *et al.* ("Lubon"). The examiner alleges that given the teaching of both the '543 patent and the '494 patent that one can secrete any biologically active protein in the urine for isolation, it would have been obvious to one of ordinary skill in the art to produce any protein of interest known in the art with a reasonable expectation of success. The examiner has added Lubon to the two Sun patents but fails to include reference to Lubon in her reasons for combining the prior art. It is interesting to note that the examiner failed to reject claims 1 and 8 directed to a protein that degrades or detoxifies organic material over any of the three cited prior art references alone, yet now combines all three of these prior art to reject claims 1 and 8. It is applicants' position that the none of the prior art discloses the transgenic expression of a protein or peptide that degrades or detoxifies organic material. Further, there is no motivation in the prior art to express such a protein. Applicants respectfully point out that the Examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining elements to make out a *prima facie* case of obviousness, the Examiner is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make the combination and (ii) a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The Examiner has failed to support the alleged case of *prima facie* obviousness and failed to show all of the elements of the claims.

All of the claims are now directed to the transgenic expression of a protein or a peptide that degrades or detoxifies organic material and a transgenic animal that expresses a protein or peptide that degrades or detoxifies organic material. In view of these amendments, it is requested that this rejection be withdrawn.

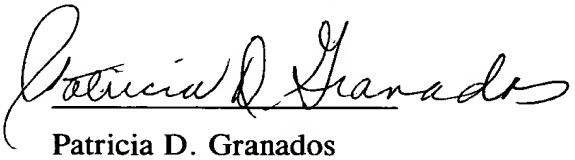
7. Claims Free of the Prior Art

It is noted that the examiner states that claims 52, 53, 62 and 63 are free of the prior art, however, claims 52 and 62 were rejected as anticipated over the two Sun patents. A clarification is kindly requested.

Conclusion

In light of the foregoing amendments and remarks, applicants submit that all claims are in condition for allowance, and they solicit an early indication to that effect. Should the examiner believe that further discussion of any remaining issues would advance the prosecution, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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Date

Patricia D. Granados
Reg. No. 33,683

FOLEY & LARDNER
Suite 500
3000 K Street, NW
Washington, D.C. 20007-5109
(202) 672-5300